

REMARKS

Applicants respectfully request that the foregoing amendments be made prior to examination of the present application.

Support for the amendments to claim 6 can be found, for example, in Examples 23, 24, 40 and 45.

Support for the amendments to claim 11, can be found, for example, in Examples 16-20.

Support for new claim 15 can be found, for example, in Examples 17 and 18.

Support for new claim 16 can be found, for example, in original claim 6 and at page 17, line 34 to page 18, line 25.

Support for new claim 17 can be found, for example, in Example 16.

Support for new claim 18 can be found, in original claim 3 and at page 20, lines 13-18

Support for new claim 19 can be found, for example, in original claim 4 and at page 20, lines 19-22.

Support for new claim 20 can be found, for example, in Examples 32-44.

Support for new claim 21 can be found, for example, in Examples 41-44.

Support for new claim 22 can be found, for example, in Example 2.

Support for new claim 23 can be found, for example, at page 19, line 36, to page 20, line 3 and in Examples 8, 38 and 39.

Support for new claim 28 can be found, in original claim 3 and at page 7, lines 22-24.

Rejections Under 35 U.S.C. § 102

Claims 1-5 and 7-13 were rejected under 35 U.S.C. 102(b) as being anticipated by Mahmood *et al.* Applicants contend that for the following reasons, the amended claims are not anticipated by Mahmood *et al.*

The “marrow stromal cells” described in Mahmood *et al.*, and “mesenchymal stem cells” of the present invention are different cell populations and attach hereto are Exhibits 1-4 that support this argument.

Exhibits 1 and 2 are from an introductory textbook of embryology (Tan Langman, *Medical Embryology*, fourth edition, Williams & Wilkins, 1981; Appendix I, Chapter 5; and Appendix II, chapter 9), that teach that mesenchymal tissue is developed from mesodermal tissue during embryogenesis. As would be understood by one of ordinary skill in the art, mesodermal/mesenchymal-cell differentiation progresses in the order of mesodermal stem cells, mesenchymal stem cells, and mesenchymal cells.

Exhibits 3 and 4 support that “marrow stromal cells” are a distinct cell population from mesenchymal stem cells, which represent differentiation stage just downstream of “mesodermal stem cells”. Exhibit 3 (Majumdar *et al.*) teaches that mesenchymal stem cells and marrow stromal cells (denoted as “marrow-derived stromal cells”) are morphologically and phenotypically different. For example, please see the underlined parts in the abstract. Exhibit 4 (Kobune *et al.*) describes that stromal cells could be induced from telomerized human mesenchymal stem cells, which inherently means that stromal cells and mesenchymal stem cells are different. Given the above, applicants contend that Mahmood *et al.* does not anticipate the instant claims.

Claims 1-5 and 7-13 were rejected under 35 U.S.C. 102(b) as being anticipated by Twardzik *et al.* Twardzik *et al.* only discloses that TGF- α is useful in stimulating stem cell or precursor cell proliferation, migration and differentiation (see Abstract of Twardzik *et al.*); but does not teach or suggest the treating of a cranial nerve disease by the *in vivo* administration of mesenchymal cells. Paragraph 0102 of Twardzik *et al.* discloses that mesenchymal cells can differentiate into chondrocytes, cartilage, osteoblasts, and bones.

Paragraph 0103 describes that isolated marrow stem cells can be used in conjunction with a TGF- α polypeptide to expand the stem cell population, and that the expanded cells may be transplanted into a subject where they can differentiate into various tissues, depending on the surrounding microenvironment of the transplant site. Paragraph 0108 describes that neural stem cells are present throughout the adult rodent CNS and in the subependyma of adult human forebrain, and that TGF- α stimulates proliferation of neural stem cells and promotes migration to a site of injury or deficit, concluding that TGF- α may be useful in the treatment of CNS ischemic disease. Paragraph 0136 discloses in addition to the fact that mesenchymal progenitor cells are used in cell replacement therapy, that mesenchymal cells give rise to chondrocytes, osteoblasts, cartilage and bone. Paragraph 0138 describes that “[h]ematopoietic stem cells can be transplanted intravenously, as can liver stem cells which will locate to the liver. Neural stem cells can be transplanted directly into the brain at the site of injury or disease”. In other words, Twardzik *et al.* does not exemplify that mesenchymal cells can differentiate into neural cells, nor does it describe that mesenchymal cells administered *in vivo* have a therapeutic effect on cranial nerve diseases. Given the above, applicants believe that Twardzik *et al.* does not anticipate the instant claims.

Claims 1-8 were rejected under 35 U.S.C. 102(b) as being anticipated by Gold *et al.* Claims 1-5 have been canceled. With respect to claim 6, applicants contend that Gold *et al.* does not teach the genetically modified mesenchymal cells of claim 6 of the present application *per se*. In addition, the genetically modified mesenchymal cells showed a remarkably advantageous effect as described in Examples 27-47 of the specification.

Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Charge Authorization

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

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By  _____

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